REMARKS

Claims 1, 5, 6, 8, 9, 11 and 20-31 are pending in the instant application. Claims 1, 5, 6, 8, 9, 11 and 20-31 have been rejected. Claims 1, 11, 22, 23, 24, 25, 26, 28 and 29 have been amended. Claims 8, 9 and 21 have been canceled. Support for these amendments is provided throughout the specification, for example, in the originally filed claims and in the Examples. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of the amendments and the following remarks.

I. Rejection of Claims 21, 22, 24, 26 and 29 under 35 U.S.C. 112, first paragraph

Claims 21, 22, 24, 26 and 29 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

With respect to claims 21 and 22, the Examiner suggests that Applicant does not have support for the term about in the instantly claimed ranges. Further, the Examiner suggests that Applicants do not suggest a range comprising the two points.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have canceled claim 21 and amended claim 22 to delete the term "about". Further,

claim 22 has been amended to recite a penetration rate of bisoprolol through the skin of between 4 and 54.3 $\mu g/h \cdot cm^2$.

MPEP 2163.05, Part III makes clear that with respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A limitation in the claim to "between 35% and 60%" was found to meet the written description requirement.

In the instant application, the range described in the original specification included a range of 3-300 $\mu g/h \cdot cm^2$ (see e.g. page 6, line 6, page 7, line 12, page 8, line 22) and specific examples of 4.0 and 54.3, with additional specific examples of penetration rates in between of e.g. 4.3, 34.0, 39.6 and 45.6 (see page 28). Accordingly, amendment of the claims to recite a penetration rate of bisoprolol through the skin of between 4 and 54.3 $\mu g/h \cdot cm^2$ clearly meets the written description requirement. See MPEP 2163.05, Part III and *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

With respect to claims 24, 26 and 29, the Examiner suggests that the ranges of 4.5 to 8.5 wt.% of organic acid and/or 5 to 15 wt.% of isopropyl myristate are new matter as there is no explicit support for these instantly claimed ranges.

Applicants respectfully disagree.

With respect to the organic acid, it is respectfully pointed out that the claims have been amended to recite sodium acetate as the organic acid and/or a pharmaceutically acceptable salt thereof. The ranges described in the original specification for organic acids and/or a pharmaceutically acceptable salts thereof included a range of "0.01-20 wt.%, more preferably 0.1-15 wt.%, in particular preferably 0.1-10 wt.%" (see paragraph [0026] at page 13) and specific examples of 4.5 and 8.5, with an additional specific example of an amount in between of 5.0 of sodium acetate, are set forth in Examples 3 and 4, Example 5 and Example 2, respectively. Applicants believe one skilled in the art would consider the range of "4.5 to 8.5 wt.%" of sodium acetate inherently supported by the discussion in the original disclosure thus meeting the written description requirement. See MPEP 2163.05, Part III.

Further, with respect to the 5 to 15 wt.% range of isopropyl myristate, it is respectfully pointed out that the claims have been amended to recite "10 to 15 wt.%." The ranges described in the original specification for absorption promoters such as isopropyl myristate are set forth at paragraph [0029] on page 15 and include 0.01-40 wt.%, more preferably 0.05-30 wt.% and in particular preferably 0.1-20 wt.%, while specific examples of 10 wt.%, 15 wt. % and an amount in between of 10.5 wt. % are set forth in Examples 3 and 4, Example 5, and Examples 1 and 6, respectively. Accordingly, Applicants believe one skilled in the art would consider the range of "10 to 15 wt.%" of isopropyl myristate inherently supported by the discussion in the original disclosure, thus meeting the written description requirement. See MPEP 2163.05, Part III.

Withdrawal of these rejections under 35 U.S.C. 112, first paragraph is respectfully requested.

II. Rejection of Claims under 35 U.S.C. 103(a)

Claims 1, 5, 6, 8, 9, 11 and 20-31 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Modamio et al. (Int. J. Pharmaceutics 1998 173:141-148) in view of Hirano et al. (U.S. Patent 6,495,159), Higo et al. (U.S. Patent 5,866,157) and Heller et al. (U.S. Patent 4,710,497),

further evidenced by Walters (Transdermal Drug Delivery, 1989, New York, NY, pp 97-246).

Applicants respectfully traverse this rejection.

At the outset, it is respectfully pointed out that claim 1 has been amended to recite an adhesive patch having a pressure-sensitive adhesive layer comprising a pharmaceutically acceptable salt of bisoprolol, wherein said adhesive layer is a matrix type, and the composition thereof contains 2-ethylhexyl acrylate·vinyl acetate·acrylic acid copolymer, isopropyl myristate, and sodium acetate, and the penetration rate of bisoprolol through skin is 4-300 $\mu g/h \cdot cm^2$.

The Examiner has acknowledged in the Office Action mailed October 9, 2009 that the prior amendment of the claims overcomes the prior obviousness rejection over Modamio et al. in view of Hirano et al. and Higo et al., evidenced by Walters. Thus, claim 1, as further amended herein to recite a pressure-sensitive adhesive layer comprising a pharmaceutically acceptable salt of bisoprolol, wherein said adhesive layer is a matrix type, and the composition thereof contains 2-ethylhexyl acrylate·vinyl acetate·acrylic acid copolymer, isopropyl myristate, and sodium acetate, and the penetration rate of bisoprolol

through skin is 4-300 μg/h·cm^2, and claims dependent therefrom, must also be unobvious over the prior art combination of Modamio et al. in view of Hirano et al. and Higo et al., evidenced by Walters.

Addition of the teachings of Heller et al. to the above combination of references also fails to render obvious the instant claimed invention.

The cited combination of references still does not teach or suggest use of 2-ethylhexyl acrylate·vinyl acetate·acrylic acid copolymer as claimed. Nor does the cited combination of references teach or suggest use of this copolymer in combination with a pharmaceutically acceptable salt of bisoprolol as claimed. Further, the cited combination of references does not teach or suggest the combination of isopropyl myristate and sodium acetate, as claimed.

Accordingly, the cited combination of references does not teach or suggest all elements of the claimed invention and therefore cannot render obvious the instant claimed invention.

In addition, Applicants respectfully disagree with the Examiner's characterization of Heller et al. as teaching use of penetration enhancers in the compositions to aid in the

penetration rate of bisoprolol. Experiments of Heller et al. are related to pindolol and propranolol, not bisoprolol. While pindolol and propranolol fall within the same category of beta-blockers as bisoprolol, their chemical structures are completely different from bisoprolol. Thus, teachings of neither Heller et al. nor Modamio et al. in view of Hirano et al. and Higo et al., evidenced by Walters, provide the requisite reasonable expectation of success to the skilled artisan, with respect to isopropyl myristate enhancing the permeation rate of bisoprolol and more particularly a pharmaceutically acceptable salt thereof as claimed. Thus, the cited combination of references cannot render obvious the instant claimed invention.

Further, as evidenced by Examples 3 through 8 of the instant specification, compositions comprising both isopropyl myristate and sodium acetate as claimed exhibited a much higher percutaneous absorption rate of the bisoprolol salt as compared to Examples 1 and 2 comprising either isopropyl myristate or sodium acetate.

Applicants are also submitting herewith a Declaration by the inventor Satoshi Amano containing additional data comparing the effects of three patch compositions containing different absorption promoters on skin permeation of

bisoprolol. As discussed in paragraph 2 and shown in Table 1 of inventor Amano's Declaration, three test example patches with identical ingredients except for the absorption promoter were prepared using the procedures described in Examples 1 to 3 of the instant patent application. The patch of Test example 1 comprises ingredients in accordance with the instant claimed invention. Bisoprolol flux was examined in each patch according to the skin penetration test described in Test 1 at paragraph [0049] of the instant patent application. As shown in Table 2 and Figure 1 of inventor Amano's Declaration and discussed in paragraph 3 of inventor Amano's Declaration, the patch of Test example 1 containing isopropyl myristate as the absorption promoter in combination with sodium acetate exhibited significantly higher skin permeation of bisoprolol compared to oleyl alcohol in combination with sodium acetate (Test example 2) and isostearyl alcohol in combination with sodium acetate (Test example 3).

Achieving this significantly higher penetration rate for a bisoprolol salt with the instant claimed combination of elements of a pharmaceutically acceptable salt of bisoprolol, 2-ethylhexyl acrylate·vinyl acetate·acrylic acid copolymer, isopropyl myristate, and sodium acetate is

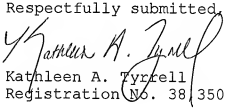
completely unexpected over teachings of the cited references and rebuts any prima facie obviousness over the combination of cited references. See MPEP 2141.

Withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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